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Review

Extracorporeal blood purification in burns: A review

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ABSTRACT

A prolonged and fulminant inflammatory state, with high levels of pro and anti inflammatory mediators, is seen after extensive thermal injury. Blood purification techniques including plasma exchange, continuous venovenous hemofiltration, and adsorbing membranes have the potential to modulate this response, thereby improving outcomes. This article describes the scientific rationale behind blood purification in burns and offers a review of literature regarding its potential application in this patient cohort.

Contents

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1. Introduction

Immune modulation by extracorporeal blood purification has been studied as a potential treatment for a variety of acute inflammatory states such as sepsis, pancreatitis, and after cardiac arrest [1,2]. Extracorporeal techniques have also been suggested to improve outcomes in patients with burns in the setting of organ dysfunction and refractory burn shock [3,4]. The purpose of this manuscript is to describe the scientific rationale behind extracorporeal blood purification, review the literature as this concept applies to the management of burn patients and review promising extracorporeal therapies.

2. Rationale for blood purification

There is a large body of evidence with respect to the inflammatory state associated with sepsis in critically ill patients [5]. This understanding may be applicable to the burn population because the genomic response in humans to inflammatory diseases is highly correlated, irrespective to the source of the insult [6]. The human response may represent a "final common pathway" that can be manipulated regardless of the source of inflammation. Therefore, our current understanding of sepsis should provide some insight into the processes related to the inflammatory state seen in burn patients. Sepsis is associated with a systemic inflammatory response syndrome (SIRS) which occurs due to increased expression of pro and anti inflammatory mediators [5,7,8]. In the early phase of SIRS, pro inflammatory cytokines predominate [5]. This is followed by a phase of high expression of anti inflammatory cytokines sometimes referred to as compensatory anti inflammatory response syndrome (CARS), which leads to immunosuppression [5,9]. It is hypothesized that this "cytokine storm" results in multiple organ dysfunction (MOD) and subsequent mortality. On the other hand, depressed or impaired cytokine production has also been seen in severe sepsis with high mortality [5]. A balanced level of inflammatory mediators seems to be necessary to survive sepsis. Based on this understanding, agents targeted to specific cytokines and key mediators have been examined in clinical trials. Interleukin 1 (IL 1) receptor antagonists, antibradykinin agents, anti tumor necrosis factor (TNF) antibodies, toll like receptor blockers and platelet activating factor receptor antagonists have been studied, but none have demonstrated a survival benefit in phase III trials [5,10,11]. Recombinant human activated protein C was the only agent to make it to market; however, it was subsequently withdrawn due to unfavorable post marketing data and lack of benefit in follow on studies [12]. A plausible hypothesis for the inability of specific targeted therapies to improve clinical outcomes is the relative complexity and redundancy of the human body, with different cytokine profiles and host pathogen interactions [13] as well as the considerable variability in responses to a severe insult. The above factors make detailed understanding and selection of therapeutics problematic. Thus, a non selective approach via extracorporeal blood purification is an attractive treatment option while the pathophysiology of the inflammatory response is elucidated. Three hypotheses exist about the possible regulation of cytokine levels. The first one, the so called "peak concentration hypothesis," states that by reducing total cytokine levels in the early pro inflammatory phase, subsequent MOD and mortality may be prevented. In contrast, the second one, called "threshold immunomodulation theory," has a dynamic view of the different compartments. By non selectively removing cytokines from the blood, cytokines from the interstitium and tissues will also be reduced because they will follow the concentration gradient until a new equilibrium is achieved. At this point, the cascade of overwhelming inflammation should stop and organ damage could be prevented. Additionally, efficiency of mediator clearance is highly dependent on the concentration of the mediator. As such, mediators that are present at higher concentrations are likely to be cleared more effectively. In the third hypothesis, the "mediator delivery hypothesis," the use of high replacement volumes may increase lymphatic flow, which helps to transport and deliver cytokines to the blood compartment where they can be removed using blood purification techniques [7,14]. Non selective blood purification does not target a specific mediator but removes cytokines based on their blood concentrations. By this approach, it is thought that abundant cytokines can be removed and a balanced state can be achieved. Still, we do not know all the components and regulation mechanisms of this complex system. One must be wary of possible unforeseen effects when modulating the inflammatory response in the face of these unknowns.

3. Pathophysiology of burns and why blood purification makes sense

Cytokines are elevated early in the course of burn injury without signs of sepsis [15 17]. Finnerty et al. examined the cytokine profile of children and adults after burn. This group found a greater inflammatory response in adults, compared to children, with high levels of IL 6, IL 8, IL 10, IL 4, IL 17, granulocyte macrophage colony stimulating factor (GM CSF) and interferon gamma (INF γ). IL 6, IL 8, IL 1β, IL 18 and IL 10 showed the highest elevations during the first week after the burn injury [18,19]. Enhanced catabolism and metabolism, which have an important impact on prolonged morbidity and mortality, are associated with high levels of pro inflammatory cytokines in burns [15,20]. The inflammatory and hypermetabolic response has been shown to begin early, within the first 24 h after the

injury, and increases quickly over the first five days [15,21]. Of note is that in addition to proinflammatory cytokines, anti inflammatory cytokines are also elevated. This inflammatory state early after burn injury, termed ''cytokine storm'' by some authors, is understood as disturbed cytokine homeostasis [8,14]. Every additional insult on top of this early inflammatory state, such as infections, sepsis and surgery, exacerbates the risk factor of MOD, which is associated with a very high mortality [22].

Rhabdomyolysis has been associated with both acute kidney injury (AKI) and mortality in the setting of burn injury [23 25].

Myoglobin, which is released from skeletal muscle after injury, is thought to contribute to the development of AKI by increasing oxygen free radical production and by precipitating with Tamm Horsfall protein in the renal tubule [26]. Early elimination of myoglobin by certain types of extracorporeal membranes might decrease the risk of renal failure and presumably subsequent MOD and death.

In summary, attempts to modulate inflammatory reac tions, regulate cytokine homeostasis, and decrease myoglobin by blood purification in the early state of burn trauma seems to be a promising therapeutic option.

4. Blood purification techniques in burns

4.1. *Plasma exchange*

Plasma exchange or plasmapheresis has been studied as a rescue therapy in burn patients failing to respond to conventional fluid resuscitation. Despite the paucity of data, plasma exchange has been advocated as a strategy in severe or refractory burn shock at selected burn centers. Small studies in this population have demonstrated a decrease in the resuscitative fluid requirement, increase in mean arterial blood pressure, increase in urine output, decrease in lactate levels, improvement of lymphocyte function, and decrease of the mixed lymphocytic reaction [27,28]. No increase in adverse events was reported in these studies. To date, there are no studies that evaluate cytokine levels during plasma exchange in burn patients. Plasma exchange has also been studied in the context of sepsis. Similar to work in the burn population, small studies have shown improved hemodynamics, but a mortality benefit has yet to be determined [29,30]. Limitations of this technique must also be considered. In plasma exchange, the entire plasma volume is removed and replaced. This results in the removal not only of pathogenic factors (e.g., cytokines) but also of beneficial factors such as coagulation factors, immu noglobulins, and other plasma proteins. By removing such components, one might actually impair an adequate physio logic response. Moreover, it is not possible to regulate the amount of each substance that is removed, harmful or beneficial, using this technique. Furthermore, plasma exchange requires replacement with fresh frozen plasma and/or albumin. Transfusion of these human derived com ponents carries the risk of infection, anaphylactic reactions, and transfusion related acute lung injury [31]. In conclusion, plasma exchange seems to be a potential therapeutic option in severe refractory burn shock, albeit one without a proven mortality benefit. Large, clinical trials are needed to determine whether plasma exchange can improve outcomes in patients with burns and sepsis.

4.2. *Continuous venovenous hemofiltration (CVVH)*

CVVH is an accepted therapy in the setting of AKI. While traditional renal replacement therapies such as hemodialysis achieve clearance by means of the diffusion of solute across a semi permeable membrane, CVVH achieves clearance by means of convection (or 'solute drag'). This is presumed to enhance the removal of water soluble middle molecular weight molecules (5 50 kDa) such as cytokines [1]. Clinical studies examining the use of CVVH as a therapy in septic patients demonstrate different results. Heering et al. showed improved hemodynamics and, while TNF α was detected in the ultrafiltrate, plasma levels of cytokines did not change [32]. A multicenter randomized trial using CVVH in septic patients and comparing it to a conventionally treated group of septic patients found a higher rate and severity of organ failure and no reduction of cytokine plasma levels [33]. It has been postulated that CVVH with high doses, so called high volume hemofiltra tion (HVHF), can lead to better results because of a higher effect of convection with enhanced removal of inflammatory med iators. In the recently published multicenter IVOIRE trial, patients with septic shock and AKI were randomized to either HVHF at 70 ml/kg/h or standard volume CVVH at 35 ml/kg/h [34]. No difference in 28 day mortality, hemodynamic profile, or organ function was demonstrated between the two groups. The authors came to the conclusion that HVHF cannot be recommended for treatment of septic shock complicated by AKI. It is important to note, however, that the study was stopped prior to the enrollment of the desired number of patients. This resulted in a low power that was insufficient to detect more subtle differences between the treatment groups [34]. Given the results of two other, large randomized controlled trials, the current recommendation is that renal replacement therapy should be prescribed at a rate of 25 ml/kg/h in patients with AKI [35,36]. There are less data regarding burn patients specifically. Our group examined, in a retrospective fashion, the early use of CVVH in severely burned patients with a total burn surface area (TBSA) >40% and AKI (as defined by the AKI Network criteria $\geq$2 [37]) [3]. The study included 29 patients treated with CVVH (doses ranged from 30 to 120 ml/kg/h) compared to a historical control group. The early use of CVVH was associated with a lower 28 day mortality and in hospital mortality compared to controls. Moreover, in patients with acute respiratory distress syndrome (ARDS), an improved ratio of partial pressure of oxygen (PaO_2) to the fraction of inspired oxygen (FiO_2) at 24 h in the CVVH group was observed. Significantly fewer patients required catecholamines at 24 and 48 h after CVVH initiation. While cytokines were not measured, the authors hypothesized that reduction of inflammatory mediators and resulting immunomodulatory effects might explain the results.

It is possible that different patient populations, severity of illness and types of organ failure might explain the differing results seen in the studies done to date. However, it is important to note that the two largest, randomized controlled trials failed to demonstrate an improvement in outcomes with a higher dose [35,36]. This implies that findings based on smaller groups are either due to type one error or that

improvements in surrogate measures (e.g., FiO_2 in patients with ARDS) are not clinically meaningful. However, the role of HVHF has not been thoroughly examined in burn patients specifically. The ''Randomized controlled evaluation of hemo filtration in adult burn patients with septic shock and acute renal failure'' (RESCUE) trial (NCT01213914) is ongoing and will address the potential utility of HVHF in the setting of burn injury. Patients in this study are randomized to treatment with HVHF at 70 ml/kg/h versus the standard care (which can include CVVH if it is dosed at <35 ml/kg/h). The primary outcome measure is total vasopressor requirement at the end of the 48 h therapy. Secondary outcome measures are PaO_2/FiO_2 ratio, vasopressor free days, survival time, days in the intensive care unit (ICU), ventilator free days, and renal recovery.

5. Emerging blood purification techniques

5.1. *Adsorptive membranes and columns*

The principle of adsorption is the binding of molecules (e.g., mediators, cytokines, antibiotics, and proteins) to a mem brane or adsorptive column on the basis of ionic charge or size. Adsorptive membranes and columns have been designed to remove cytokines in the setting of SIRS and sepsis. Some of the technologies presented below (polymethylmethacrylate and high cut off membranes) are integrated into the membrane used for renal replacement therapy. Others (such as poly myxin B and CytoSorb®) are hemoperfusion columns that can be used in conjunction with renal replacement therapy (in series with either CVVH or conventional hemodialysis) and could also be used as stand alone systems. These novel extracorporeal therapies, targeted at non specific cytokine removal, could conceivably improve outcomes in the setting of burn injury.

5.1.1. *Polymyxin B columns*

Membranes bound with the antibiotic polymyxin B have the ability to bind endotoxin. In the Early Use of Polymyxin B Hemoperfusion in Abdominal Sepsis (EUPHAS) study [38], hemoperfusion with a polymyxin B column was evaluated in patients with sepsis due to intra abdominal infection. Hemo perfusion with the polymyxin B column improved hemody namics, decreased organ dysfunction, and reduced 28 day mortality compared to controls. In the ongoing EUPHRATES study (NCT01046669), the use of a polymyxin B column in patients with septic shock and endotoxemia will be examined. The primary outcome measure is 28 day mortality, while secondary outcomes include 90 day, 6 month, and 12 month mortality.

While the specific pathogens may differ between centers, Gram negative organisms are the leading cause of life threatening infections in the setting of burn injury [39,40]. Therefore, polymyxin B columns could be a therapeutic option in burn patients with endotoxemia. Peng et al. studied the effect of CVVHD with polymyxin B immobilized fibers in septic burn patients (TBSA ≥50%) [41]. Plasma levels of endotoxin, IL 1ß, IL 6, IL 8 and TNF α were significantly decreased by this therapy. Outcomes could not be assesed given the small number of patients involved.

5.1.2. *PMMA membranes*

Polymethylmethacrylate (PMMA) membranes have been shown to be able to remove cytokines effectively [42], and clinical studies have shown an improvement in hemody namics [2,43]. Regarding burn patients, Nakae et al. [44] reported on three cases with severe burn injury (TBSA >30%) treated with CVVH utilizing a PMMA membrane and found reduction in IL 6 levels in all three patients. Matsuda et al. compared the use of continuous hemodiafiltration with PMMA membrane vs. intermittent hemodialysis in patients with ARDS and renal failure [45]. They found a higher 28 day cumulative survival rate in the PMMA group. The PMMA membrane also resulted in a significant reduction in IL 6 levels.

5.1.3. *Cytokine-adsorbing columns*

Cytokine adsorbing columns are designed expressly for the non selective removal of cytokines [2,46]. They are composed of beads designed to capture and adsorb cytokines by size exclusion chromatography and nonselective hydrophobic interactions. Small molecules, below 10 kDa, travel through the pores of the beads while larger molecules and cells, above 50 kDa, pass around the beads. These columns have demon strated the ability to reduce cytokines in vitro and improve mortality in animal models [47 50].

The column CytoSorb® has been tested in a multicenter randomized controlled study including 43 patients with sepsis and acute lung injury. Results of this study were presented recently [51]. Use of the cytokine adsorbing column signifi cantly reduced IL 6, MCP 1, IL 1ra, and IL 8 levels. IL 10 and endotoxin do not seem to be removed in patients by CytoSorb®. While mortality did not differ between the two groups, the study was not powered for this endpoint. The CytoSorb® filter has also been demonstrated to efficiently remove myoglobin in vitro [52] and is a promising therapy for rhabdomyolysis that occurs in conjunction with thermal injury. A study of this technology in the setting of cardiopulmonary bypass is ongoing (NCT NCT01879176) and a study in trauma and burn patients with rhabdomyolysis is in the planning phase.

5.2. *High-cutoff membranes*

High cutoff (HCO) membranes have an in vivo cutoff point of 50 60 kDa. Most manufacturers recommend the use of these membranes with hemodialysis, which would result in cytokine removal primarily by diffusion. A decrease in IL 6 concentrations in septic patients with AKI (RIFLE class failure [53]) has been observed [54] as well as removal of middle weight molecules such as ß2 microglobulin and cystatin C [55]. However, the preliminary results of the ''High Cut Off Sepsis (HICOSS) study'' did not show a difference in mortality, duration of ICU stay, or need for catecholamines using the HCO membrane SepteX® compared to conventional contin uous venovenous hemodialysis in patients with septic shock and AKI [2]. While use of these membranes in hemofiltration mode can increase albumin losses, some authors propose the use of HCO membranes with hemofiltration to improve cytokine removal by means of convective clearance [2,56]. A reduction of norepinephrine dose and a high clearance for IL 6 was shown in a pilot study using a HCO membrane in

Table 1 – Examples, technical details, and studies for a selection of membranes designed for cytokine removal.

Name	SepteX® Gambro	oXiris® Gambro	PMMA different Toray membranes	Polymyxin B Toraymyxin®, Toray	CytoSorb® CytoSorbents	CPFA® Bellco
Type	High cutoff membrane	Adsorptive membrane	Adsorptive membrane	Adsorptive membrane	Adsorbing column	Coupled plasma filtration and adsorption
Use	As CRRT in sepsis manufacturer recommends CVVHD; study planned in CVVH	As CRRT in sepsis Use in CVVH or CVVHDF modes	As CRRT In different modes	Sepsis/endotoxemia hemoperfusion	Cytokine hemoperfusion	In multi organ failure and/or sepsis CPFA
Fibers	Polyarylether sulfon	Acrylonitril + natrium methallyl sulfonat copolymer + polyethylenimin	Polymethylmetha crylate	Polymyxin B covalently immobilized; polystyrene derived	Cross linked divinylbenzene/ polyvinylpyrrolidone beads	Reverse phase styrenic polymer resin
Surface	1.1 m^2	1.5 m^2	1 2.1 m^2	N/A	850 m^2/g	600 800 m^2/g
Studies/reviews in burn patients	N/A Might play a role in removing myoglobin [2,23]	N/A	Case report [44] reduction of IL 6	Reduction of endotoxin, IL 1ß, IL 6, IL 8, and TNF α; no different outcomes compared to no treatment [41]	N/A Might be able to remove myoglobin	N/A
Studies/reviews in septic patients	Greater relative decrease of IL 6 than with high flux membrane [54] Preliminary results of HICOSS no difference in mortality, duration of ICU stay, need of catecholamines compared to conventional CVVHD membrane [2]	No studies in humans	Removed cytokines ef fectively and improved hemodynamics (CHDF mode) [43]	EUPHAS: improved hemodynamics, organ dysfunction, 28 day mortality in intra abdominal Gram negative infections [38]	CytoSorb's European Sepsis Trial: reduction in IL 6, MCP 1, IL 1ra and IL 8. No IL 10, 28 day, and 60 day mortality reduction. No removal of endotoxin [51]	Improved hemodynamics (CPFA + HD) compared to CVVHDF; may restore leukocyte responsiveness [58]

hemofiltration mode [57]. A study of 76 patients with shock and AKI (Study Comparing High Cut off Haemofiltration With Standard Haemofiltration in Acute Renal Failure, NCT00912184) has been completed but is yet to be published. Regarding burn patients, HCO membranes are seen as a possible important therapy in rhabdomyolysis [2,23].

5.3. *Coupled plasma filtration adsorption*

In coupled plasma filtration adsorption (CPFA), plasma is separated from the whole blood by a plasmafilter, and only the plasma is passed through the adsorption cartridge. The treated plasma is then returned and the whole blood passes a hemofilter or hemodialyser. Performing adsorption only on plasma might decrease platelet aggregation and clotting problems, thus allowing a longer contact time to the adsorbent with lower flows [1]. In one study of septic patients, CPFA with hemodialysis led to improved hemodynamics compared to CVVHDF and it was postulated that it restored leukocyte responsiveness [58]. Plasma levels of cytokines, however, were not reduced. A study of 350 patients with septic shock (COMPACT 2, NCT01639664) is ongoing and is expected to complete enrollment in 2016. There are no studies in burn patients regarding CPFA.

Table 1 gives an overview of adsorptive membranes and columns.

6. Selective Cytopheretic Device (SCD)

The Selective Cytopheretic Device (SCD) is another emerging technique of immunomodulation to alter excessive acute inflammatory response. It targets activated leucocytes, which are major contributors to the inflammatory response as they produce inflammatory mediators and have phagocytotic activity. The SCD is a cartridge containing bundled polysulfone fibers. Blood passes around these fibers at a low velocity, and the circuit is designed in such a way that shear forces are low. Leukocytes adhere to the surface. Citrate anticoagulation is required for this technique, which results in a low ionized calcium environment that causes subsequent deactivation of leucocytes. It is thought that this modulates the SIRS response [59 61]. This device has been used in two pilot studies in patients with AKI secondary to acute tubular necrosis with the cartridge connected in series to a CRRT circuit. One study of 9 patients revealed a mortality of 22.2% compared to a case matches historical control group mortality of 77.8% [60]. Another study of 35 patients showed a mortality of 31.4% and renal recovery in all surviving patients at day 60, compared to historical mortality rates of >50% for patients with AKI who require renal replacement therapy in the ICU [61]. A larger trial, the ''Efficacy Study of a Selective Cytopheretic Device (SCD) in Patients with Acute Kidney Injury'' (NCT01400893), is ongoing, with an estimated enrollment of 344 patients.

7. Conclusion

Blood purification in burns for non specific removal of inflammatory mediators seems most likely to be effective in the early stages after injury. Based on our current understanding of sepsis and the dysregulated inflammatory response, this might lead to improvements in morbidity and mortality. Adsorbing membranes and columns like PMMA and cytokine adsorbing columns seem to be particularly promising in the early stage of burn injury without AKI, whereas polymyxin B has a special ability to remove endotoxin in the setting of Gram negative infection. The SCD has so far been used only in patients with AKI, but they could offer immunomodulation in burn patients as well.

We believe that extra corporeal blood purification has the potential to revolutionize treatment for a variety of critically ill patients, including those with thermal injury. However, further investigations in both animal models and human clinical studies (including large prospective studies) are required to further elucidate the role of these therapies.

Conflict of interest statement

The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the Department of the Army, Department of the Air Force or the Department of Defense. KL, IJS and AIB received funding to test the CytoSorb in animals as part of the SBIR phase II study awarded to CytoSorbents Corporation, Monmouth Junction, NJ. IJS and KKC received an Air Force grant (AFMSA/SG9 Grant, EM I 12 015) to evaluate Cytosorb in the treatment of rhabdomyolysis. KC is the principal investigator for the RESCUE trial (NCT01213914).

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